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CASE REPORT

Resolution of left ventricular postinfarction thrombi in patients undergoing percutaneous coronary intervention using rivaroxaban in addition to dual antiplatelet therapy

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SUMMARY

Left ventricular (LV) thrombus is usually seen in situations with reduced LV function, and is mostly seen in patients with large anterior ST-elevation myocardial infarction (MI). Most embolic events, in patients with LV thrombus formation, occur within the first 3–4 months, thus the recommendations regarding the duration of anticoagulant therapy. According to guidelines, an oral vitamin K antagonist, warfarin, is being used as an anticoagulant for this period. Novel oral anticoagulants were found to be either non-inferior or superior compared with warfarin in prevention of thromboembolism in patients with non-valvular atrial fibrillation. However, the data about their role in the management of LV thrombus are limited to case reports. Here, we report on the dissolution of LV apical thrombus in 3 patients with anterior ST-elevation MI receiving dual antiplatelet therapy and rivaroxaban on a reduced dose for 3 months.

BACKGROUND

Left ventricular (LV) thrombus is usually seen in situations with reduced LV function, and is mostly seen in patients with large anterior ST-elevation myocardial infarction (MI) with anteroapical aneurysm formation.¹ Many of these patients will have an LV apical aneurysm with akinesis or dyskinesis. In most cases, thrombus is located within or adjacent to the LV apex¹ but can also occur with large inferolateral infarctions/aneurysms.

In observational studies and meta-analyses, most embolic events, in patients with LV thrombus formation, occur within the first 3–4 months, thus the recommendations regarding the duration of anticoagulant therapy.^{2–6}

According to guidelines, an oral vitamin K antagonist (VKA), warfarin, is being used as an anticoagulant for this period.^{7 8}

Novel oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, etc) were found to be either non-inferior or superior compared with warfarin in prevention of thromboembolism in patients with non-valvular atrial fibrillation.⁹ However, the data about the role of NOACs in the management of LV thrombus are scarce and mostly limited to case reports.

Here, we report on the dissolution of LV apical thrombus in three patients with anterior ST-elevation MI receiving dual antiplatelet therapy

(DAPT) and rivaroxaban on a reduced dose (15 mg) for 3 months.

CASE PRESENTATION**Case 1**

A Caucasian male aged 52 years was admitted with retrosternal chest pain evolving during the past 5 days. The ECG showed a subacute anterior STEMI with marked ST elevation and Q waves in leads V2–V6.

Transthoracic echocardiography revealed an anteroapical severe hypokinesia with an EF of 35% and an apical sessile thrombus which was confirmed using contrast (figure 1).

HAS-BLED score was 1 point.

The coronary angiogram revealed a total occlusion of the midpart of the left anterior descending coronary artery (LAD) and collateral circulation from the right coronary artery. The vessel was treated using newer-generation drug-eluting stent (Resolute Onyx stents, 3.5 Å~ 26 mm) with a good angiographic final result.

HAS-BLED score was 1 point.

Case 2

A Caucasian male aged 75 years was admitted with a left-sided thoracic chest pain that started 4 hours prior to presentation. The ECG showed an acute anteroapical ST-elevation MI with subtle ST elevation in leads V2–V4.

Coronary angiography revealed a tight proximal LAD disease that was directly stented using an everolimus 4 Å~ 18 mm drug-eluting stent with great angiographic final result. DAPT was started using acetylsalicylic acid (150 mg/day) and prasugrel (10 mg/day).

Transthoracic echocardiography was performed 3 days after the percutaneous coronary intervention and revealed a penduculated apical thrombus measuring 1.6×1.7 cm (figure 2) in an akinetic distal anteroapical area and hypokinetic anteroapical segment with an estimated EF of 35–40%.

HAS-BLED score was 2 points.

Case 3

A Caucasian female aged 69 years was admitted with an epigastric pain that started 11 hours prior to presentation. The ECG showed an acute anterolateral ST-elevation MI with ST elevation in leads V1–V6, I, aVL.



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Figure 1 Contrast echocardiography study confirmed the presence of an apical sessile thrombus and a severe anteroapical hypokinesia with an EF of 35%.



Figure 3 Transthoracic echocardiography revealed a pedunculated and elongated apical thrombus measuring 2.5×1.8 cm and a severely anteroapically hypokinetic left ventricle with an EF of 30%.

Coronary angiography revealed a tight proximal to mid-long LAD disease that was directly stented using an everolimus 4 Å~32 mm drug-eluting stent with great angiographic final result. DAPT was started using acetylsalicylic acid (75 mg/day) and ticagrelor (180 mg/day).

Transthoracic echocardiography was performed 4 days after the percutaneous coronary intervention and revealed a pedunculated and elongated apical thrombus measuring 2.5×1.8 cm (figure 3) and a severely anteroapically hypokinetic LV with an EF of 30%.

HAS-BLED score was 2 points.

TREATMENT

Regarding the patient reported in case 1, DAPT was initiated with acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day), while a reduced dose of rivaroxaban (15 mg/day) was given in order to limit the bleeding risk (triple therapy). At 1 month, echocardiography was repeated and revealed complete dissolution of the thrombus, despite persistence of the apical akinesia. The triple therapy was continued for another 2 months.

Regarding the patient reported in case 2, low dose of rivaroxaban was initiated (15 mg/day), while prasugrel was switched to clopidogrel (75 mg/day) and aspirin to 75 mg/day in order again to reduce the bleeding risk as possible. At 1 month, echocardiography was repeated and revealed complete dissolution of the thrombus and normal LV systolic function. Again, and in concordance with the guidelines that refer to VKA after acute coronary syndrome and LV thrombus formation, the above triple

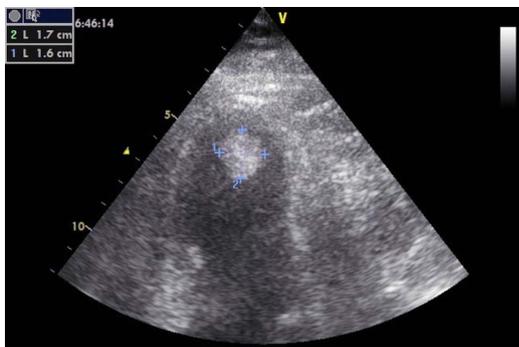


Figure 2 Transthoracic echocardiography revealed a pedunculated apical thrombus measuring 1.6×1.7 cm in an akinetic distal anteroapical area and hypokinetic anteroseptal segment with an estimated EF of 35–40%.

therapy (DAPT+rivaroxaban 15 mg/day) was continued for a total of 3 months.

The patient on case 4 was started on rivaroxaban (15 mg/day), and ticagrelor was replaced by clopidogrel (75 mg/day). At 2 weeks, echocardiography was repeated and revealed complete dissolution of the thrombus and an improved LV systolic function (EF 40–45%).

Again, the above triple therapy was continued for a total of 3 months.

OUTCOME AND FOLLOW-UP

All three patients received a triple therapy that consisted of low dose of rivaroxaban (15 mg/day), and DAPT (aspirin 75–100 mg/day plus clopidogrel 75 mg/day) for a total of 3 months. In all patients, complete dissolution of the thrombi was evident by repeat echocardiography study in 2 weeks–1 month. Follow-up for a year was uneventful for all three cases.

DISCUSSION

Rivaroxaban is an oral inhibitor that binds directly to factor Xa. It is currently approved for the treatment of deep venous thrombosis, non-valvular atrial fibrillation and pulmonary embolism.^{9–12}

Azizi *et al*¹³ describe a case of postinfarction LV thrombus dissolution using a combination of DAPT (aspirin 100 mg/day plus clopidogrel 75 mg/day) plus rivaroxaban for 3 months; nevertheless, the daily dose of rivaroxaban they used was 20 mg/day. We, however, used the low dose of rivaroxaban (15 mg/day) for the reasons we will advocate further down.

Ventricular thrombi have been successfully treated using novel anticoagulant, either in cases of old myocardial infarction, where dabigatran was used (220 mg/day),¹⁴ or in cases of LV thrombus secondary to tachycardia-induced heart failure using rivaroxaban 15 mg/day.¹⁵

Rivaroxaban was also used for treating a case of intraventricular thrombus in Chagas disease¹⁶ and in a setting of dilated cardiomyopathy where again 15 mg/day was used.¹⁷

Similarly, reported cases have shown the effectiveness of apixaban as well, in the resolution of left atrial thrombus.¹⁸

Another case report described the growth of a left atrial appendage thrombus, despite well-conducted treatment with a VKA, which then disappeared during treatment with rivaroxaban 15 mg/day.¹⁹ In this report, repeated TEE showed a markedly increased giant thrombus mass in the LAA under well-controlled VKA therapy for 6 weeks. After that, the authors decided to switch the oral anticoagulation to

rivaroxaban based on the increasing evidence that VKAs had a poor capability to resolve large intracardiac thrombi. This novel direct acting factor Xa inhibitor is reported to have the potential not only to prevent a thrombosis but also to resolve established thrombi by direct inhibition of free and thrombus-associated Factor Xa.²⁰ Note that in a congestive heart failure rat model, rivaroxaban reduced platelet activation by attenuating the secondary phase of ADP-induced platelet aggregation.²¹

In the reported cases, we demonstrate LV thrombus dissolution using a rivaroxaban 15 mg/day in the setting of acute coronary syndromes that forced administration of DAPT.

In general, in the setting of ACS, triple therapy with DAPT and NOACs is associated with at least a doubling of the risk of major bleeding, as similarly reported for VKAs in the WOEST trial²² and consistent with the nationwide registry data from Denmark.²³ Therefore, there is no strong evidence to suggest that NOACs behave differently to VKAs in the setting of ACS or stenting.

Thus and even though data are limited, the principle of continuing an existing NOAC seems reasonable at present as stated by the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA).²⁴ It is also stated at the same paper that when VKA is given in combination with clopidogrel and/or low-dose aspirin, the dose intensity of VKA should be carefully regulated, with a target INR range of 2.0–2.5 (Class IIa) and where an NOAC is used in combination with clopidogrel and/or low-dose aspirin, the lower tested dose for stroke prevention in AF (ie, dabigatran 110 mg two times per day, rivaroxaban 15 mg o.d. or apixaban 2.5 mg two times per day) may be considered (Class IIb).

Thus, our decision to use the low dose of rivaroxaban stated (15 mg/day).

In the setting of patients requiring oral anticoagulation after percutaneous coronary intervention, the European Society of Cardiology²⁵ states that triple therapy should be limited in duration, depending on the clinical setting, thromboembolic (CHA₂DS₂-VASc) score and bleeding risks (HAS-BLED) score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol). The duration depends on the individual risk for ischaemic and bleeding events.

The use of prasugrel or ticagrelor as part of triple therapy should be avoided, given the lack of established benefit and the greater risk of major bleeding compared with clopidogrel.

In a prospective observational study of 377 patients who underwent drug-eluting stent placement and who had an indication for OAC, 5.6% received prasugrel and the rest clopidogrel.²⁶ All patients were treated with triple therapy for at least 6 months. The primary end point of thrombolysis in MI major and minor bleeding occurred more often in the prasugrel group (28.6% vs 6.7%).

In an analysis of the TRANSLATE-ACS study with 11 756 MI patients, 526 (4.5%) were discharged on triple therapy that included aspirin, clopidogrel and warfarin and 91 (0.8%) on triple prasugrel, aspirin and warfarin therapy.²⁷ Triple therapy of the prasugrel arm was associated with a greater risk of any bleeding events compared with the triple-clopidogrel arm.

Gastric protection should be implemented with a proton-pump inhibitor.

Triple therapy using an NOAC could be hazardous and only a few studies have investigated triple therapy, including an NOAC

in patients suffering from coronary artery disease and non-valvular atrial fibrillation.

In the APPRAISE-2, apixaban was combined with aspirin and clopidogrel in 81% of patients, and led to a significant increase in fatal and intracranial bleeding without clinical benefit.²⁸

In ATLAS ACS 2, low-dose rivaroxaban (2.5–5 mg two times per day) was administered with aspirin and clopidogrel in 92% of patients. This was associated with a 16% reduction in the composite efficacy end point (cardiovascular death, myocardial infarction and stroke) and a small increase in major bleedings.²⁹

The twice daily 2.5 mg dose of rivaroxaban resulted in significantly lower rates of all-cause and cardiovascular mortality, which was not observed with the twice daily 5.0 mg dose.

The HAS-BLED score was 1–2 for the abovementioned patients, who had normal creatinine clearance and based on the above as well as on observational studies and meta-analyses, that report that most embolic events, in patients with LV thrombus formation, occur within the first 3–4 months, we decided to use rivaroxaban 15 mg/day in addition to DAPT (aspirin 75 mg/day plus clopidogrel 75 mg/day) for a total of 3 months.

All patients had complete thrombus resolution and no bleeding complications.

Learning points

- ▶ Short-duration rivaroxaban at a low dose (15 mg/day) in combination with a dual antiplatelet therapy (DAPT) was effective for the treatment of left ventricular (LV) thrombus in patients with acute coronary syndromes and drug-eluting stent implantation, and at low to intermediate bleeding risk.
- ▶ Randomised controlled trials are needed to confirm these encouraging observational data, and to possibly confirm the optimal low dosage of NOACs when associated with DAPT, demonstrating that these molecules can effectively replace VKAs in the treatment of post-STEMI LV thrombi in patients undergoing percutaneous coronary intervention.

Competing interests None declared.

Patient consent Obtained.

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